DEPARTMENT OF HEALTH AND HUMAN SERVICES

FEB - 1 1994

Our Reference Numbers: 91-0054 and 91-0055

Brian D. Bollwage, J.D.
ENZON, Inc.
40 Kingsbridge Road
Piscataway, NJ 08854-3998

Dear Mr. Bollwage:

Enclosed is Department of Health and Human Services Establishment License No. 1171, issued to ENZON, Inc., with corporate address at 40 Kingsbridge Road, Piscataway, New Jersey, with locations at Bedford, Ohio and South Plainfield, New Jersey, in accordance with the provisions of Title III Part F of the Public Health Service Act of July 1, 1944 (58 Stat. 702) controlling the manufacture and sale of biological products. This license authorizes you to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce those products for which your establishment holds unsuspended and unrevoked product licenses issued by the Department of Health and Human Services.

Also enclosed is a product license authorizing your establishment to manufacture and ship for sale, barter and exchange in interstate and foreign commerce Pegaspargase. Under this license you are authorized to manufacture Pegaspargase utilizing Asparaginase (for Further Manufacturing Use) manufactured by Merck, Sharp, and Dohme, Division of Merck & Co., Inc. (U.S. License No. 2) under a shared manufacturing arrangement.

The product will be marketed in 5 ml single use vials and will be indicated for use in combination chemotherapy for the treatment of patients with acute lymphoblastic leukemia who are hypersensitive to native forms of L-asparaginase.

You are requested to submit samples of product in final containers of each future lot together with protocols showing results of all applicable tests. No lots of product shall be distributed until notification of release is received from the Director, Center for Biologics Evaluation and Research.

The dating period for this product shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the day in which the enzyme is reacted with the activated polyethylene glycol. We acknowledge your commitment to maintain an ongoing stability program. Results of ongoing stability studies should be submitted throughout the dating period as they become available.

Any changes in the supplier of the licensed Asparaginase (for Further Manufacturing Use), or in the manufacture, testing, packaging or labeling of Pegaspargase or in the manufacturing facilities (including the contract manufacturing facilities) will require the submission of a Supplement to either your Product or Establishment License Application for our review and written approval prior to implementation. Any addition or deletion of establishments involved in the shared manufacturing arrangement may require the submission of appropriate supporting data in order to ensure continued compliance with the approved standards for the manufacture of Pegaspargase.

Your establishment and product licenses also provide for the filling and packaging of Pegaspargase by [redacted] All manufacturing operations performed at [redacted] shall be under your direct control and supervision.

We acknowledge your commitment to implement active postmarketing surveillance of adverse events occurring after treatment as outlined in your letter of January 6, 1994. You are also requested to submit adverse experience reports in accordance with the requirements for postmarketing reporting of adverse drug experiences (21 CFR 314.80) until such time that specific reporting requirements for biological products become effective. All experience reports should be prominently labeled as "Biological Product" and be submitted to the attention of Biostatistics and Epidemiology, HFM-210, Office of Establishment Licensing and Product Surveillance, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information. In addition, advertising and promotional labeling should be submitted for review and approval prior to the initial publication of any advertisement and prior to the initial dissemination of any promotional labeling. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics and Research.

Please acknowledge receipt of the enclosed license to the Director, Division of Vaccine and Related Products Applications, HFM-475, Center for Biologics Evaluation and Research and of the enclosed establishment license to the Director, Division of Establishment Licensing, HFM-205, Center for Biologics Evaluation and Research.

Sincerely yours,

Jerome A. Donlon, M.D., Ph.D.
Director
Office of Establishment Licensing
and Product Surveillance
Center for Biologics
Evaluation and Research

Sincerely yours,

M. Carolyn Hardegree, M.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research